REMARKS

Claims 1-43 were pending; claims 19-36 have been withdrawn from examination as a result of a requirement for restriction under 35 U.S.C. §121. Claims 1-18 and 37-43 are under examination.

Claims 1-18 and 37-43 were rejected under 35 U.S.C. §112, first paragraph. Claim 37 was rejected under 35 U.S.C. §102(e) and Claims 39-41 were rejected under 35 U.S.C. §103.

Claims 7, 18, 41, 42 and 43 have been canceled and claims 1, 4-6, 8, 11, 15, 16 and 37-39 have been amended herein without prejudice or disclaimer of any previously claimed subject matter.

Support for the claim amendments is found throughout the specification. For example, support for the amendment to claim 1 is found, *inter alia*, on page 6, lines 16-19 and page 12, lines 2-3. Support for the amendment to claim 37 is found, *inter alia*, on page 18, lines 21-24 and support for the amendment to claim 38 is found, *inter alia*, on page 19, lines 24-25. Thus, no new matter has been added.

The amendments are made solely to promote prosecution without prejudice or disclaimer of any previously claimed subject matter. With respect to all amendments and canceled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any objection and/or rejection made by the office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or embodiments in one or more future continuation and/or divisional applications.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is entitled "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**".

Applicants have carefully considered the points raised in the Office Action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Rejections under 35 U.S.C. §112, first paragraph

Claims 1-18, 38, 42, and 43 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Applicants respectfully traverse these grounds for rejection.

The Examiner asserts that "the specification does not teach how to use the method to produce a therapeutic effect" and states that "[a]lthough dopamine **antagonists** have been shown to be effective in treating the symptoms of schizophrenia, the effect of dopamine **replenishment** in specific areas of the brain is not known" (Office Action, page 3, original emphasis). The Examiner also asserts that "it is not a routine matter to produce dopamine or any other biologically active molecule at the desired level in the desired location using *ex vivo* gene therapy or cell-based therapies" (Office Action, page 4) and that "methods of transplantation of neural tissue or other cells into the CNS are not routinely successful" (Office Action, page 5). Applicants traverse these assertions.

The claimed invention is directed to a method for providing dopamine or a dopamine precursor to a subject with schizophrenia through administering therapeutic cells to the prefrontal cortex of the subject's brain. The therapeutic cells, which produce dopamine or a dopamine precursor, are administered adhered to a support matrix and in an amount effective to alleviate a negative symptom of schizophrenia.

As is known in the art, and pointed out by the Examiner, negative symptoms of schizophrenia are associated with a hypodopaminergic state in the frontal cortex. The Examiner, citing Seibyl et al. (U.S. Patent No. 5,447,948), points out that the art teaches that "mesofrontal dopamine deficits may be implicated in the negative symptoms of schizophrenia (Column 1, lines 44-57)" and that "the complex pathophysiology of schizophrenia includes both increased dopamine tone (in mesolimbic dopamine tracts) and decreased dopamine tone (in mesofrontal dopamine tracts)" (Office Action, paragraph bridging pages 3-4). Thus, the art indicates that

dopamine deficits in the prefrontal cortex have been detected in subjects with schizophrenia and have been specifically associated with negative symptoms of schizophrenia.

Use of cells which produce biologically active molecules adhered to support matrix, as described in the present invention, have been successfully administered to deliver the biologically active substance to a particular location in a brain and such administration has resulted in a therapeutic effect. For example, administration of retinal pigment epithelial cells (dopamine producing cells) attached to a support matrix to the post-commissural putamen of brains of advanced Parkinson's disease patients in a phase I/II study resulted in improved motor function in all patients.[1] Also, administration of dopamine producing cells adhered to a matrix microcarriers to rodent and non-human primate models of Parkinson's disease resulted in long term amelioration of parkinsonian motor behavioral deficits.[2] Thus, contrary to the Examiner's assertions regarding "the unpredictable state with regard to gene therapy and cell-based therapies" (Office Action, page 6), administration of cells as described in the present invention has been successful in the amelioration of a deficit dopaminergic state at particular locations in the brain.

The specification teaches administration of a composition comprising cells which produce dopamine or a dopamine precursor to the prefrontal cortex of a patient with schizophrenia and that the composition, with the cells adhered to a support matrix, is administered in an amount effective to alleviate a negative symptom of schizophrenia (see, for example, page 12, lines 1-6, and page 22, lines 12-13). The specification also describes art-accepted "negative symptoms" of schizophrenia and standard methodology by which the symptoms may be assessed, for example, at page 7, line 21, to page 8, line 4. The specification

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[1] See, Watts et al. (2001) XIV International Congress on Parkinson's Disease, Helsinki, Finland, Abstract and Poster P-305, submitted herewith.

[2] See, for example, U.S. Patent No. 5,618,531, of record; Potter et al. (1997) Abstracts Soc. for Neuroscience, 778.10, submitted herewith; Subramanian et al. (1998)Abs. Amer. Soc. for Neural Transpl., 2-5, submitted herewith; Subramanian et al. (1998) Abs. 5th International Cong. Parkinson's Disease and Movement Disorders, New York, submitted herewith; Subramanian et al. (1999) Parkinsonism and Related Disorders, 5, S111, submitted herewith.

thus describes how to determine administration of an amount of the claimed composition effective to alleviate a negative symptom of schizophrenia (see, for example, page 23, lines 2-11, and lines 22-31).

The specification teaches a variety of therapeutic cells that produce dopamine or a dopamine precursor, a variety of support matrices and how such cells are adhered to the support matrices. See, for example, page 12, line 26, to page 19, line 25, and page 19, line 26, to page 22, line 6.

Thus, Applicants submit that the specification teaches how to make and use the claimed invention and that the pending claims are in compliance with the enablement requirements.

Accordingly, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. §102(e)

Claim 37 was rejected under 35 U.S.C. §102(e) as allegedly being anticipated by U.S. Patent No. 5,750,103 (Cherksey). Applicants respectfully traverse this rejection, to the extent that it is applied to the pending claims.

Claim 37 of the instant invention is directed to a pharmaceutical composition comprising therapeutic cells and Sertoli cells, wherein the cells are adhered to a support matrix. Claim 38 is directed to a pharmaceutical composition comprising therapeutic cells, protective cells and support cells, wherein the cells are adhered to a support matrix.

The Examiner asserts that "Cherksey specifically discloses retinal pigment epithelial (RPE) cells and chromaffin cells adhered to the surface of a support matrix (see Claims 1 and 7)" (Office Action, page 7). Claim 1 of Cherksey is a Markush-type claim wherein the composition comprises viable cells adhered to a support matrix and the type of cell is selected from a list of cell types.

Applicants submit that Cherksey does not describe compositions comprising more than one type of cell as claimed in the instant invention.

Thus, as it does not teach or suggest every element of the pending claims, Cherksey cannot anticipate the present invention. Accordingly, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 102(e).

Rejections under 35 U.S.C. §103

Claims 39-41 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over U.S. Patent No. 5,750,103 (Cherksey). Applicants respectfully traverse this rejection, to the extent that it is applied to the pending claims.

As with the rejection under 35 U.S.C. §102(e), the Examiner asserts that "Cherksey specifically discloses retinal pigment epithelial (RPE) cells and chromaffin cells adhered to the surface of a support matrix (see Claims 1 and 7)" (Office Action, page 8). The Examiner also asserts that it "would have been obvious to put the cells and the support matrix in suitable packaging (as recited in Claim 39) or separate containers (as recited in Claim 40) to produce a kit" (Office Action, page 8).

Cherksey, however, does not teach or suggest all of the necessary elements of the pending claims. Claim 39 of the instant invention is directed to a kit for use in providing dopamine or a dopamine precursor to a subject with schizophrenia where the kit comprises therapeutic cells, protective cells, support cells and a support matrix. Cherksey does not describe or suggest compositions comprising the combination of cell types, nor use of the combination of cell types, as claimed in the instant invention. Thus, Cherksey does not teach all of the limitations of the pending claims.

Accordingly, the cited reference does not support *prima facie* obviousness with regard to the claimed invention. Applicants respectfully request withdrawal of the rejection of claims 39-41 under 35 U.S.C. §103.

CONCLUSION

Applicants believe that all issues raised in the Office Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact Applicants' agent at the telephone number below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 311772000600. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

AMENDMENTS

Please enter the following amendments without prejudice or disclaimer.

In the Claims:

Please cancel claims 7, 18, 41, 42 and 43.

Please amend claims 1, 4-6, 8, 11, 15, 16 and 37-39 as follows.

1. (Amended) A method for [treating negative symptom of] providing dopamine or a dopamine precursor to a subject with schizophrenia [in a subject], comprising administering [an effective amount of] a cell/support complex to the prefrontal cortex of the subject's brain, [comprising therapeutic cells to a site in said subject's brain,] wherein said cell/support complex comprises therapeutic cells [which produce dopamine or a dopamine precursor adherent] adhered to a [first] support matrix, wherein said therapeutic cells produce dopamine or a dopamine precursor [thereby alleviating said symptoms] and wherein said cell/support complex is administered in an amount effective to alleviate a negative symptom of schizophrenia.

4. (Amended) The method of claim 1 wherein said [first] support matrix is made of material selected from the group consisting of glass, polystyrene, polypropylene, polyethylene, polyvinylidene fluoride, polyurethane, polyalginate, polysulphone, polyvinyl alcohol, acrylonitrile polymers, polyacrylamide, polycarbonate, polypentene, polypentane, acrylonitrile polymer, nylon, magnetite, natural polysaccharide, modified polysaccharide, collagen, gelatin and modified gelatin.

5. (Amended) The method of claim 4, wherein said [first] support matrix is gelatin or modified gelatin.

6. (Amended) The method of claim 5 wherein said [first] support matrix is crosslinked gelatin.

8. (Amended) The method of claim 1, wherein the therapeutic cells are selected from the group consisting of retinal [pigmented] pigment epithelial cells, [human foreskin fibroblasts,] chromaffin cells, cells of neural origin, paraneural cells, cells engineered by somatic cell hybridization, cells derived from the adrenal medulla, and cells that have been genetically engineered to express [a biologically active compound] dopamine or a dopamine precursor.

11. (Amended) The method according to claim 8 wherein the therapeutic cells are retinal [pigmented] pigment epithelium (RPE) cells.

15. (Amended) The method of claim 1 wherein said cell/support complex further comprises protective cells adherent to a [second] support matrix.

16. (Amended) The method of claim 15 wherein said cell/support complex further comprises support cells adherent to a [third] support matrix.

37. (Amended) A pharmaceutical composition comprising therapeutic cells and [protective cells] Sertoli cells, wherein the cells are adhered to a support matrix.

38. (Amended) [The] A pharmaceutical composition [of claim 37, wherein said composition further comprises] comprising therapeutic cells, protective cells and support cells, wherein the cells are adhered to a support matrix.

39. (Amended) A kit suitable for use in [treating the symptoms of] providing dopamine or a dopamine precursor to a subject with schizophrenia, comprising in a suitable packaging:

therapeutic cells that produce dopamine or a dopamine precursor;

protective cells;

support cells; and

a support matrix, wherein the cells can be adhered to the support matrix.